Original Article

Randomized open comparative trial of dexamethasone–cyclophosphamide pulse and daily oral cyclophosphamide versus cyclophosphamide pulse and daily oral prednisolone in pemphigus vulgaris

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ABSTRACT

Background: In various case series, pulse therapy has shown good results in pemphigus vulgaris (PV), with long-term remissions. **Aims:** To compare the efficacy and side-effects of dexamethasone–cyclophosphamide pulse and daily oral cyclophosphamide (DCP+C) versus cyclophosphamide pulse and daily oral prednisolone (CP+P) in PV. **Methods:** Twenty-eight active PV patients were randomized to receive either DCP with daily oral cyclophosphamide (Group A, n = 15) or CP with tapering doses of daily oral prednisolone (Group B, n = 13) for 12 months and followed-up for at least 3 months after stopping therapy. They were compared for time taken to achieve mucocutaneous disease control, achieve remission, relapse during treatment period, relapse after stopping therapy and side-effects. **Results:** Of 28 cases, 25 (Group A - 15, Group B - 10) completed the study period and were analyzed. The time for initiation of cutaneous response and time to achieve complete disease remission were significantly lesser in group B. However, other efficacy parameters were comparable. In Group A, significant adverse events were dysgusea, hiccups, palpitation, nail discoloration, bone pain and urinary tract infection while in Group B, they included nausea, moon facies, flushing, secondary amenorrhea, steroid withdrawal symptoms and dyspnea due to weight gain. **Conclusions:** Early remission was achieved in group B but the relapse rates during the treatment phase or after stopping therapy were comparable. Both therapies had comparable side-effect profiles, although Group B showed greater steroid-induced adverse events.

Key words: Pemphigus vulgaris, Pulse therapy, Dexamethasone, Cyclophosphamide

INTRODUCTION

Pemphigus vulgaris (PV) is a relatively common autoimmune vesicobullous disorder in India with a mortality of >90% if untreated.[1] The prognosis has dramatically improved with the use of systemic corticosteroids and various anti-inflammatory and immunosuppressive agents. However, prolonged daily therapy required to achieve a good control of PV is associated with several distressing side-effects. Pulse therapy (administration of a suprapharmacological dose of a drug over a short period at a fixed interval), initiated with the aim of completely suppressing the cyclical proliferation of immunocompetent cells, gave a new vision to the treatment of pemphigus.[2] Since the advent of the fixed dose, fixed duration regimen of dexamethasone–cyclophosphamide pulse (DCP) with daily oral cyclophosphamide (DCP + C regimen) for PV in India in 1983 and its subsequent modification (addition of daily oral steroid in the initial stage in very active cases), long-term remissions have been reported in large case series of patients.[3] However, this therapy carries the disadvantage of prolonged (3 days each month) hospital stay, with high-dose dexamethasone

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being associated with certain distressing side-effects like flushing, hiccups, generalized weakness lasting 1–2 weeks after each pulse and secondary infections.

Another pulse regimen comprising of intravenous cyclophosphamide pulse (CP) with daily oral prednisolone (CP + P regimen) has also shown encouraging results in PV in an open trial.[4] This regimen circumvents the disadvantage of DCP in being a 1 day a month therapy, thus significantly reducing the number of workdays lost due to therapy, resulting in better treatment compliance. The degree of immunosuppression is also reduced. Several studies have shown encouraging results with intravenous cyclophosphamide pulse in other autoimmune diseases with fewer side effects than daily oral cyclophosphamide, especially with regard to urinary bladder malignancies and gonadal toxicity.[5,6] Intermittent high-dose therapy with CP probably impairs immune surveillance for relatively short periods compared with daily therapy and therefore the malignant potential of CP would be lower.

We undertook this study to compare the efficacy and side-effects of these two regimens in PV.

METHODS

We conducted a randomized prospective open clinical trial. Twenty-eight cases of PV of either sex, aged 25–70 years, were inducted. Enzyme-linked immunosorbent assay (ELISA) test for anti-desmoglein 1 and 3 antibodies was performed. Unmarried patients or those who had not completed their family, patients on immunosuppressive therapy within 8 weeks or anti-inflammatory agents within 4 weeks of randomization, severe renal or hepatic disease, active peptic ulcer, inherited or acquired immune deficiency, cases with chronic or frequent drug-resistant infections or bone marrow insufficiency were excluded.

Baseline hematological and biochemical investigations, weight and blood pressure measurements were carried out and repeated during each follow-up visit. Electrocardiogram (ECG) and chest X-ray were undertaken before starting treatment and repeated at 6 months and 1 year. ECG was also carried out if a patient reported of cardiac symptoms. Urine cytology for detection of bladder malignancy and bone densitometry (DEXA scan) for steroid-induced osteoporosis was not performed.

Informed written consent was obtained from all study patients. Approval for conducting the study was obtained from our ethics committee.

Patients were randomized into the following two groups, the randomization numbers being computer generated from the website www.http://randomizer.org:

Group A (DCP + C): Dexamethasone–cycloposphamide pulse (DCP) with daily oral cyclophosphamide

Hundred milligrams of dexamethasone dissolved in 500 ml of 5% dextrose given as slow IV infusion over 2 h and repeated on three consecutive days combined with 500 mg cyclophosphamide in the same infusion on any one of the three days, preferably on the second day. Such DCP were repeated at 4 weeks. They also received cyclophosphamide 50 mg orally per day. Additional oral prednisolone (0.5–0.75 mg/kg/day) was added after 2 weeks of initiation of therapy (first follow-up visit) if initial disease activity was not controlled with DCP + C (patient developing ≥5 new lesions/day).

Group B (CP + P): Cyclophosphamide pulse (CP) with daily oral prednisolone

IV cyclophosphamide (15 mg/kg/day) on one day every 4 weeks along with daily oral prednisolone (starting dose of 1.5 mg/kg/day, tapered to 1 mg/kg/day after 2 weeks and then by 10 mg every 4 weeks after disease remission, until maintenance dose of 10 mg/day was reached, which was maintained until the end of therapy). Patients were advised to increase their daily water intake to at least 3 L/day for 3 days, starting a day before pulse. Cyclophosphamide pulse was followed by hydration with 500 ml of 5% dextrose or normal saline. They were advised not to hold urine and to void on urge. All patients were given sodium 2-mercaptoethanesulphonate (MESNA) at a dose of 60% of cyclophosphamide in the same infusion. Oral ondansetron (8 mg) was administered if the patient complained of severe nausea and vomiting. All patients on daily steroids were given calcium carbonate + vitamin D (500 mg) twice a day and pantoprazole 40 mg once a day.

The total period of therapy was 12 months. Patients were evaluated bi-weekly during the first 1 month and then four-weekly. In patients achieving remission within 1 year, treatment was stopped and they were followed-up for at least 3 months to look for relapses.

The primary efficacy parameter was time to achieve disease remission, i.e. significant re-epithelization of at least 80% of the lesions. Secondary efficacy parameters included time to initiation of response, i.e. stoppage of appearance of new lesions, time to develop relapse while on therapy, time to develop relapse after stopping therapy and adverse events.

Stastical analysis

Data analyses were performed using χ^2 or Fisher's exact test, when appropriate, and Student's *t*-test. A *P*-value less than 0.05 was considered significant.

RESULTS

In Group A, all cases ($n = 15$) completed the treatment and follow-up phase while in Group B, ($n = 13$), 10 continued in the study while three were lost to follow-up (moved abroad - 1, left against advice - 1, reason not known - 1). The baseline demographic profile and clinical characteristics of patients in both groups are presented in Table 1.

Response to treatment [Table 2]

Time for initiation of cutaneous response

The development of new skin blisters stopped after 2–20 weeks (mean 7.33 weeks) in Group A and 2–8 weeks (mean 3.16 weeks) in Group B, the difference being statistically significant ($P = 0.02$).

Time for initiation of mucosal response

New mucosal lesions stopped developing in 2–28 weeks (mean 6.67 weeks) in Group A and 2–16 weeks (mean 6 weeks) in Group B, $P = 0.79$.

Time for significant re-epithelization of cutaneous lesions (cutaneous remission)

The time taken for significant re-epithelization of skin lesions in Group A was 2–20 weeks (mean 8.92 weeks). In Group B, it was 2–16 weeks (mean 5.66 weeks) ($P = 0.197$).

Time for significant re-epithelization of mucosal lesions (mucosal remission)

In Group A, mucosal remission was achieved in 2–40 weeks (mean 12.5 weeks) and in Group B in 2–16 weeks (mean 9.55 weeks) ($P = 0.432$).

Total number of patients who achieved remission

Nine of 15 patients (60%) in Group A and six of 10 patients (60%) in Group B achieved remission ($P = 0.68$) and they remained in remission for the rest of the study period, i.e. until the completion of 12 pulses.

Time to achieve remission

The patients in Group A took 4–40 weeks (13 ± 9.2 weeks) and in Group B, 2–16 weeks (8.4 ± 3.2) to achieve remission, the difference being statistically significant ($P < 0.001$).

Number of patients who had recurrence during the treatment period

Five cases (33.3%) in Group A and four (40%) in Group B achieved remission initially but later, within the treatment period, developed new mucocutaneous lesions, $P = 0.86$. The average time for recurrence in both the groups was approximately 20 weeks.

Number of patients who relapsed after stopping treatment

In Group A, eight patients and in Group B, six completed more than 3 months of follow-up. Five of eight (62.5%) in Group A and four of six (66.6%) in Group B relapsed in a mean time period of 14 and 12.6 weeks, respectively, after stopping treatment, $P = 1.0$.

Number of patients who received additional daily prednisolone for control of disease in Group A

Six of 15 patients (40%) in Group A required additional daily steroid to control the initial disease activity for a mean period of 8–22 (15 ± 4.69) weeks.

Pre- and posttreatment antidesmoglein level after 12 pulses

The antidesmoglein antibody levels in patients in both groups, who remained in remission, were significantly reduced from the pretreatment level. There was no statistically significant difference in the pre- and posttreatment levels of antidesmoglein 1 and 3 between the two groups [Table 2].

Table 1: Profile of pemphigus vulgaris patients

	Group A (n = 15)	Group B (n =13)	*P*-value
Age (years)	25-68	34-62	0.678
Sex:	(46.93 ± 13.93)	(44.62 ± 9.02)	
Male	1	4	
Female	14	9	
Duration of disease	0.6-24 months (8.21 ± 7.02)	1.5-42 months (9.57 ± 11.31)	0.945
Sites of involvement			
Pure cutaneous	1	1	
Pure mucosal	2	1	
Mucocutaneous	12	11	

Table 2: Response to treatment in the study groups

	Group A (n = 15)	Group B (n = 10)	*P*-value
Initiation of cutaneous response	2–20 weeks (6.30 ± 6.625)	2–8 weeks (3.16 ± 1.80)	0.02
Initiation of mucosal response	2–28 weeks (6.67 ± 7.16)	2–16 weeks (6 ± 4.56)	0.79
Time for cutaneous remission	2–20 (8.92 ± 7.772) weeks	2–16 (5.666 ± 3.73) weeks	0.197
Time for mucosal remission	2–40 (12.5 ± 11.82) weeks	2–16 (9.55 ± 6.27) weeks	0.432
No. of patients who achieved remission during the study period	9/15 (60%)	6/10 (60%)	0.68
Time to achieve remission (weeks)	4–40 (13 ± 9.2)	2–16 (8.4 ± 3.2)	<0.001
Patients who had recurrence during the treatment period	5 (33.3%)	4 (40%)	0.86
Onset of relapse while on treatment (weeks); range (mean ± SD)	8–28 (20 ± 6.8)	8–32 (20.8 ± 5.4)	0.30
No. of patients relapsed after therapy	5/8 (62.5%)	4/6 (66.6%)	1.0
Time for posttreatment relapse in weeks; mean (range)	14 ± 4.9 (3–44)	12.6 ± 3.5 (1–32)	1.0
Pre-/posttreatment mean antidesmoglein antibody levels			
anti dsg1	75.96/23.602	102.88/17.48	
anti dsg3*	138.33/35.871	138.44/32.27	

*The cut-off value for anti-dsg 1 and 3 is 20.0

Adverse events

The side-effects are summarized in Table 3.

In Group A, dysgeusea was significantly more while hiccups, palpitation (ECG normal), nail discoloration, bone pain and episodic urinary tract infection (UTI) were the exclusive side-effects. In Group B, nausea and moon facies were significantly more than Group A while flushing, menstrual irregularity, steroid withdrawal symptoms and dyspnea due to weight gain were exclusively seen in this group. Of the steroid-related side-effects, dyspnea due to weight gain and moon facies were significantly more in Group B, weight gain, posterior subcapsular cataract and steroid-withdrawal symptoms were also higher in this group (although not statistically significant) while dyspepsia, epigastric pain, hyperglycemia, hypertension and pyoderma were comparable in both the groups. Among the investigational abnormalities, anemia and leucocytosis were significantly more in Group B. There was no significant difference in other investigational abnormalities [Table 4]. Elevation in blood urea, creatinine and *serum glutamic oxaloacetic transaminase* (SGOT) observed in few cases was mild and transient and did not necessitate treatment modification or stoppage.

DISCUSSION

This was a study of 1 year duration to compare the treatment efficacy (remission rate, control of disease) and side-effects between the two pulse therapy regimens. DCP + C is a widely used modality for this disease in India since 1983.[3] Several case series establishing its efficacy in PV have been reported, although no randomized controlled trials have been undertaken. CP + P has also shown encouraging results in few studies, is devoid of distressing side-effects of high-dose dexamethasone in DCP and hospital stay is also reduced.[7]

In our study, time taken to achieve remission was significantly lesser in the CP + P than in the DCP + C group, besides an early initiation of cutaneous response, although the number of cases achieving remission in both the groups were comparable. This may be attributed to high initial daily prednisolone doses in the CP + P group. However, the other treatment-response parameters like initiation of mucosal response, relapse during therapy and posttreatment relapse were comparable.

Various studies from India on DCP have shown disease remission in 40–100% of the cases after 8–48 months of therapy, which is similar to that in our Group A patients (60% cases showed remission after 12 months of therapy).[8-13] However, the majority of these patients required maintenance therapy of daily oral cyclophosphamide to achieve sustained remission. In our study, more than 60% of the cases in both the groups relapsed after stopping therapy, which suggests that maintenance therapy is warranted in both the groups to avoid relapse. DCP carries the advantage over daily immunosuppressive therapy in having lower relapse rates and steroid-induced side-effects, although time taken to achieve remission is comparable. Akhtar *et al*. (1998), in 72 patients of pemphigus, evaluated the efficacy and safety of either prednisolone alone

Table 3: Side-effects in the study groups

	Group A (n = 15)	Group B (n = 10)	*P*-value
Nausea	5 (33.3%)	7 (70%)	0.058
Vomiting	5 (33.3%)	6 (60%)	0.136
Flushing	0	1 (10%)	0.4
Palpitation	1 (6.66%) (ECG normal)	0	0.98
Anxiety	3 (20%)	3 (30%)	0.82
Hiccups	4 (26.66%)	0	0.14
Headache/reeling of the head	5 (33.33%)	2 (20%)	0.86
Arthralgia	5 (33.33%)	2 (20%)	0.51
Weakness	7 (46.6%)	3 (30%)	0.39
Dysgeusea	7 (46.6%)	1 (10%)	0.02
Dyspepsia	5 (33.33%)	2 (20%)	0.5
Epigastric pain	3 (20%)	2 (20%)	0.79
Hyperglycemia	8 (53.3%)	5 (50%)	1.0
Hypertension	4 (26.6%)	3 (30%)	1.0
Nail discoloration	3 (20%)	0	0.25
Menstrual irregularity	0	1/6 (16.67%) (n = 6 females in the premenopausal age group)	0.40
Secondary amenorrhea	3/7 (42.8%) (n = 7 females in the premenopausal age group)	5/6 (83.3%) (n = 6 females in premenopausal age group)	0.19
Weight gain: no. of patients, range in kg (mean)	10 (66.61%) 2–11 kg (6.3)	10 (100%) 4–15 kg (9.3)	0.17
Urinary tract infection (episodic)	4 (26.6%)	0	0.12
Pyoderma	2 (13.33%)	1 (10%)	1
Dyspnea due to weight gain	0	4 (40%)	0.016
Reduced visual acuity (due to steroid-induced cataract)	1 (6.675%)	3 (30%)	0.26
Diffuse hair fall	2 (13.33%)	3 (30%)	0.35
Moon facies	1 (6.67%)	8 (80%)	0.0003
Bone pain (osteopenia)	1 (6.675)	0	1
Steroid-withdrawal symptoms	0	2 (20%)	0.15

Table 4: Investigational abnormalities in the study groups

	Group A: 15	Group B: 10	*P*-value
Anemia	4 (26.66)	7 (70)	0.048
Leucocytosis	7 (46.66)	10 (100)	0.007
Leucopenia	1 (6.66)	0	1.0
Pyuria	5 (33.33)	3 (30)	1.0
Bacteriuria	1 (6.66)	0	1.0
Hypoglycemia	0	1 (10)	0.40
Hyperglycemia	8 (53.33)	5 (50)	1.0
↑Urea	1 (6.66)	2 (2)	0.54
↑Creatinine	1 (6.66)	0	1.0
↑SGOT	2 (13.33)	3 (30)	0.35
Microscopic hematuria (>5 RBCs/HPF)	0	0	NS

Figures in parentheses are in percentage

(n = 40), prednisolone plus azathioprine (n = 15) or betamethasone–cyclophosphamide pulse therapy (BCP), with no significant difference between the groups with respect to time taken to achieve disease control. But, the frequency of relapse was higher in patients treated with steroid alone.[14] In a recent study by Shahridi-Dadras *et al*. of 123 PV patients randomized to receive either methylprednisolone–cyclophosphamide pulse or daily prednisolone with azathioprine, cutaneous remission occurred in 92.8 and 80.8% in the two groups while mucosal remission was achieved in 82.2 and 72.3% of the cases, respectively, at 12 months.[15] Rates of complete remission and relapse and major organ-specific complications were similar. However, total orally administered prednisolone, admission duration and annual weight increments were significantly lesser in the pulse group.

Cyclophosphamide, an alkylating agent, inhibits the lymphopoietic cells without affecting the hematopoietic cells. In a high dose, it is selectively toxic to B lymphocytes, with regenerating B lymphocytes being more sensitive than resting cells.

CP inhibits cyclical production of antibody-producing B lymphocytes in autoimmune diseases. CP has shown encouraging results in several autoimmune disorders like autoimmune thrombocytopenic purpura, systemic lupus erythematosus (SLE), lupus nephritis, multiple sclerosis, Wegner's granulomatosis, polyarteritis nodosa and Behcet's disease, unresponsive to daily immunosuppressives, especially corticosteroids.[7] Comparative trials have also shown greater improvement than with daily steroids. Good to excellent results have also been achieved within 2–11 months in recalcitrant PV.[4,16-18] In these patients, the dose of concomitantly administered daily oral prednisolone could be reduced to 5–10 mg or even stopped in few cases. Hence, addition of pulse significantly reduces the total cumulative dose of daily steroid. A preliminary trial from our center showed complete remission in 82% of mild to moderate PV in 12 months, with prednisolone being stopped in six of 11 cases.[18] In our patients also, we were able to reduce daily steroid to 10 mg in a majority of our cases.

Patients in both groups experienced immediate and delayed side-effects. The main side-effects observed with DCP + C were weight gain, hyperglycemia, generalized weakness, dysgusea, nausea, vomiting, dyspepsia, headache, hiccups, hypertension, UTI (episodic), nail discoloration, amenorrhea and hair fall. This was comparable to the side-effects noted in other studies, which included flushing (53.4%), hiccups (1–6.1%), dysgeusea (13%), cushingoid features (4%), diffuse hair loss (29%), weight gain (11%), candidial (8–100% in one study) and pyogenic infection (3–100% in one study), generalized weakness (2.7%), arthralgia (33.3%), hyperglycemia (none in one study to 18%), amenorrhea (2.7%), hypertension (none in one study to 3–11%), bradycardia (58%) and steroid psychosis.[8-13] Uncommonly, serious side-effects such as atrial fibrillations, ventricular arrhythmias, myocardial ischemia and cardiac arrest have been observed with this therapy, which, however, were not encountered in our patients. We strictly excluded unmarried patients or those who had not completed their family because gonadotoxicity is a well-recognized side-effect of cyclophosphamide.

In the CP + P group, the major adverse events in our study were nausea and vomiting, which were controlled with antiemetics, generalized weakness, secondary amenorrhea, diffuse hair fall and anemia. There were many side-effects attributable to concomitant daily prednisolone administration in this group, including reduced visual acuity due to posterior subcapsular cataract, hyperglycemia, weight gain, dyspnea due to weight gain, moon facies, hypertension and leucocytosis (100%). No patient experienced hematuria (due to concomitant MESNA administration in all cases) or leucopenia. In other studies, patients on CP developed nausea and vomiting (44.4–100%), leucopenia (22.2%) and microscopic hematuria (0–11.53%), which cleared with the coadministration of MESNA, amenorrhea (11.5–25%), weight gain (38.5%) and cataract (7.7%) (due to the coadministration of daily prednisolone).[4,16-18] On comparing the two groups, in Group A, dysgeusea, hiccups, palpitation, nail discoloration, bone pain and UTI were more common while in Group B, nausea, flushing, menstrual irregularity, secondary amenorrhea, dyspnea due to weight gain, moon facies and steroid withdrawal symptoms were more common. Steroid-associated side-effects were more in Group B, chiefly due to daily prednisolone.

To conclude, early remission was achieved with CP + P, but the relapse rates during the treatment or follow-up period were comparable. In both treatment groups, relapse rates were high (>60%). This highlights the need for long-term maintenance therapy in PV to prevent relapses. Both therapies had comparable side-effect profiles, although Group B showed greater steroid-induced adverse events. Because PV is a relatively common and distressing condition in India, it would be worthwhile to plan a long-term study with a larger sample size, longer follow-up for evaluation of chronic adverse effects (such as incidence of urinary bladder malignancy with chronic use of cyclophosphamide pulse, comparison of chronic side-effects of dexamethasone in pulse versus daily prednisolone), assessment of quality of life and patient acceptability of the regimens.

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